

## Spectral Evidence for the Formation of Quinone Methide Intermediates from 5- and 7-Hydroxyflavonoids

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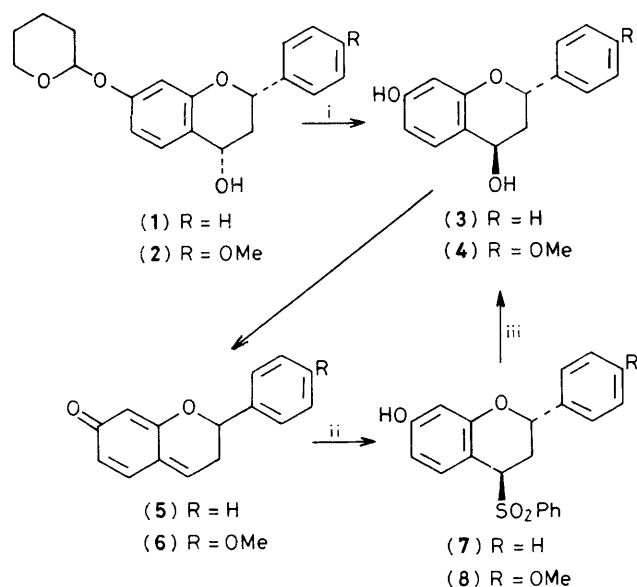
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The u.v. spectra of 5- and 7-hydroxyflavan-4-ols in acid solution are interpreted in terms of the  $\pi$ - $\pi^*$  transition of quinone methide intermediates; the enhanced reactivity of 4-substituted 7-hydroxyflavans compared to 4-substituted 7-methoxyflavans supports this mechanism which may be operative in the biosynthesis of polyflavonoids (e.g. condensed tannins).

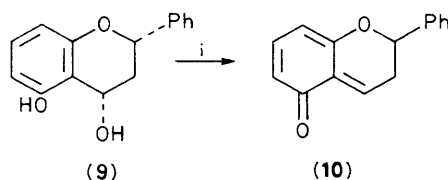
Having observed that an ethereal solution of 2,3-*trans*-7-hydroxy-3,4-*cis*-dibenzoyloxy-3',4'-dimethoxyflavan decomposes in contact with silica whereas 2,3-*trans*-3,4-*cis*-dibenzoyloxy-3',4',5,7-tetramethoxyflavan is stable under the same conditions, we decided to examine other 4-substituted 7- and 5-hydroxyflavans. It seemed likely that a flavonoid quinone methide, e.g. (5), (6), or (10), could be an intermediate in the reactions of such compounds and could account for the observed enhanced reactivity. Haslam<sup>1</sup> has suggested that quinone methides may play a part in the biosynthesis of polyflavonoids from 5- and 7-hydroxyflavonoids, although this view has been questioned by Botha *et al.*<sup>2</sup> who consider that the available evidence is consistent with carbocations as

intermediates in the acid-catalysed polymerisation of 4-substituted flavans. In a recent communication Hemingway and Foo<sup>3</sup> concluded that the occurrence of flavonoid quinone methide intermediates could account for the rapid condensations of 4-substituted 5- and 7-hydroxyflavonoids in alkaline solutions. We now report spectral evidence in addition to evidence from enhanced reactivity for the formation of such quinone methide intermediates.

We have synthesised 7-tetrahydropyranyloxyflavan-4 $\beta$ -ol (1) and its 4'-methoxy analogue (2). Removal of the tetrahydropyranyl group from the 4 $\beta$ -ol (1) by careful treatment with acid gave 7-hydroxyflavan-4 $\alpha$ -ol (3), the stereochemistry at the 4-position being that expected after treatment of a 4 $\beta$ -ol



**Scheme 1.** Reagents: i,  $\text{H}_3\text{O}^+$ ; ii,  $\text{PhSO}_2\text{H}$ ; iii, aq.  $\text{NaOH}$ -dioxane,  $20^\circ\text{C}$ . All compounds are racemic. Relative stereochemistry is shown here and in Scheme 2.

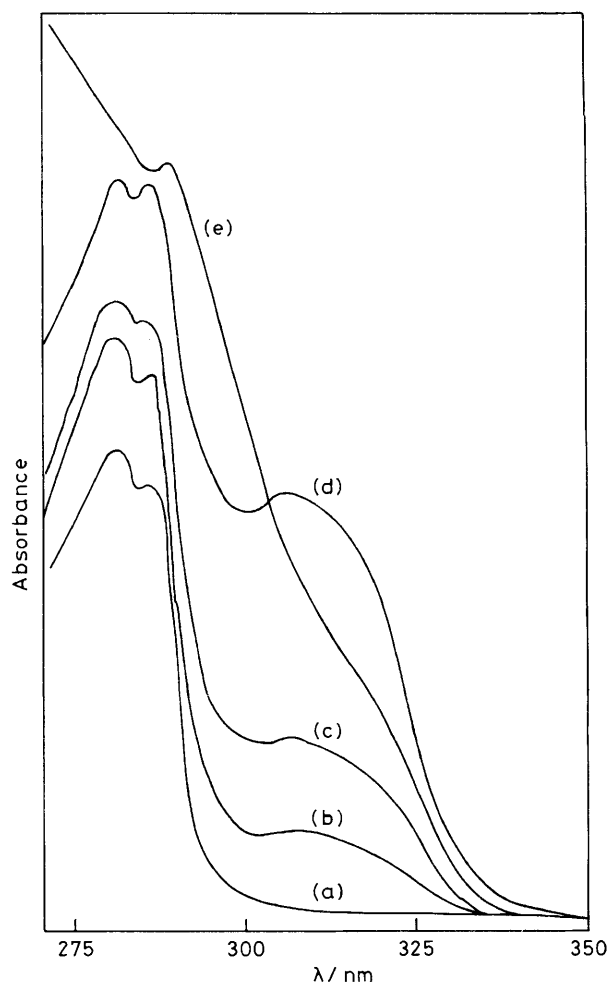


**Scheme 2.** Reagent: i,  $\text{H}_3\text{O}^+$ .

with acid.<sup>4</sup> Demethylation of 5-methoxyflavan-4-one<sup>5</sup> and reduction with sodium borohydride gave 5-hydroxyflavan-4β-ol (9).

Solutions of the 7-tetrahydropyranyloxy-4β-ols (1) and (2) in aqueous dioxane absorb at 280 and 286 nm in the ultraviolet. On addition of hydrochloric acid, a band was observed in each solution at 305 nm which gradually increased in intensity to a maximum in 3–4 h (see Figure 1). We believe that this is the result of hydrolysis of the tetrahydropyranyl ethers (1) and (2) (Scheme 1) and the formation of equilibrium concentrations of quinone methides (5) and (6) by elimination of water from the 7-hydroxyflavan-4α-ols (3) and (4). The band at 305 nm is in the range quoted for other *p*-quinone methides<sup>6</sup> and is in agreement with estimates from the application of Woodward's rules.<sup>7</sup> On the addition of an excess of sodium benzenesulphonate to the solutions of the quinone methides, the band at 305 nm gradually disappeared and after 8 h a band at 289 nm due to the sulphones (7) and (8) and a band below 275 nm from the excess of benzenesulphinic acid were apparent; the band at 305 nm had become indistinct (see Figure 1). Treatment of 3',4',7-trihydroxyflavan-4β-ol with acid similarly caused the appearance of a band at *ca.* 305 nm in about 4 h. Treatment of 5-hydroxyflavan-4β-ol (9) with acid caused, in about 19 h, the appearance of a band at 395 nm from the  $\pi$ - $\pi^*$  transition of the *o*-quinone methide (10).<sup>8</sup> The addition of sodium benzenesulphonate caused the band to disappear. In contrast to the 5- and 7-hydroxyflavan-4-ols, 7-methoxyflavan-4β-ol, which cannot form a quinone methide, showed no change in its u.v. spectrum when a solution of it in aqueous dioxane was acidified.

Several reactions of the 4-ols and 4-sulphones confirm the occurrence of quinone methides as intermediates. 7-Tetra-



**Figure 1.** U.v. spectra of 7-tetrahydropyranyloxyflavan-4β-ol (a), in aqueous dioxane; (b–d) after addition of  $\text{HCl}$ ; (b), 30 min after; (c), 1 h after; (d), 3 h after; (e) 20 min after addition of sodium benzenesulphonate.

hydropyranyloxyflavan-4β-ol (1) reacted completely with benzenethiol in acidic aqueous dioxane at room temperature in 1.5 h to give 7-hydroxy-4α-phenylthioflavan, whereas 7-methoxyflavan-4β-ol was unchanged under the same conditions after 1.5 h. This striking difference in reactivity is an indication that 7-hydroxyflavan-4α-ol (3) from the tetrahydropyranyl compound (1) is not reacting through a carbocation as would 7-methoxyflavan-4β-ol,<sup>9</sup> but through another reactive intermediate such as the quinone methide (5).

We have also found, as did Hemingway and Foo,<sup>3</sup> that in alkaline solution 7-hydroxyflavonoids only show the reactivity expected of quinone methides when they carry a good leaving group at the 4-position. 7-Hydroxy-4α-phenylsulphonylflavan (7) is completely destroyed in less than 30 min by sodium hydroxide in aqueous dioxane at room temperature. 7-Hydroxyflavan-4α-ol (3) (15%) was the only monomeric product isolated. This reaction is so rapid that we have not been able to observe the u.v. spectrum of the quinone methide intermediate; the u.v. spectrum of 7-hydroxy-4α-phenylsulphonyl-4'-methoxyflavan (8) (265, 273, 281, and 289 nm in ethanol) was replaced by a spectrum with one band at 283 nm and shoulders at 290 and 277 nm within 45 seconds when a few drops of 2M-sodium hydroxide were added. By contrast, 7-methoxy-4α-phenylsulphonylflavan,<sup>9</sup> which cannot form a quinone methide, was quite stable to sodium hydroxide in aqueous dioxane at room temperature.

From this evidence we conclude, in agreement with Hemingway and Foo,<sup>3</sup> that the formation of quinone methide intermediates constitutes a viable mechanism for the condensation of 4-substituted flavans over wide range of pH values.

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